General

Guideline Title

Lymphoma.

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Lymphoma. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 86 p. (Clinical practice guideline; no. LYHE-002). [373 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Hematology Tumour Team. Lymphoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Sep. 78 p. (Clinical practice guideline; no. LYHE-002).

Recommendations

Major Recommendations

Diagnosis and Pathologic Classification

An excisional lymph node biopsy of the largest regionally involved lymph node is the optimal specimen for initial diagnostic assessment. Similarly, a sizable biopsy from the organ of origin in extranodal lymphomas is also suitable. Compelling clinical contraindications to an open biopsy should be present before considering any other options. A careful clinical examination or radiological investigations for more accessible or palpable pathologic adenopathy, and the results of a bone marrow staging biopsy could be useful in decision making prior to opting for a lesser diagnostic specimen. In general, fine needle aspirate biopsies and biopsies of secondarily involved tissue sites are regarded as suboptimal for the initial diagnosis of lymphoma. These latter specimens do provide excellent material for evaluating possible relapse, clarification of staging at questionable sites and as a source of additional specimen where required for further special testing or research. Occasionally, multiple needle core biopsies may supply adequate tissue but this needs to be assessed on a case by case basis. Whenever possible, a reference lymphoma pathologist should confirm the diagnosis; this is particularly important in cases when only a core needle biopsy is available.

Table 1 in the original guideline document describes the histologic subclassification of the malignant lymphomas, and is an adaptation of the most recent World Health Organization (WHO) classification. This classification is based on the light microscopic interpretation complemented by special stains, immunophenotyping, cytogenetics and other information as available. The specific lymphomas are divided into three major groups, according to the degree of clinical aggressiveness, for treatment planning. All B-cell lymphomas should be immuno-phenotyped to determine if they are CD20 positive.

Required Immunohistochemical and FISH Testing for Lymphoma

In general, guidelines for immunohistochemical and fluorescence in situ hybridization (FISH) testing outlined in the most recent version of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues should be followed so as to confirm a specific diagnosis and provide necessary prognostic and/or predictive information. In addition, the following are recommended by the Alberta Provincial Hematology Tumour Team:

1. Classical Hodgkin Lymphoma: The immunohistochemical panel may include CD45/CD3/CD20/CD30/CD15/PAX5/MUM1 and should be selected on a case by case basis at the discretion of the hematopathologist. Epstein-Barr virus (EBV) studies by in situ hybridization (Epstein-Barr virus encoded ribonucleic acid [EBER]) may be considered if difficulty exists diagnostically, as most cases of the mixed-cellularity subtype of classical Hodgkin lymphoma are EBER positive.
2. Diffuse Large B-cell Lymphoma (DLBCL):
    - Immunohistochemical panels to distinguish between activated B-cell (ABC) type and germinal centre (GC) type have serious limitations (regardless of which algorithm is employed) and do not accurately subclassify many cases of DLBCL when compared to gene expression profiling. Therefore, routine use of immunohistochemical stains for the express purpose of subtyping ABC versus GC is not recommended. Relevant stains may be performed if considered of diagnostic importance by the reporting hematopathologist.
    - EBER and CD5 expression confer worse prognosis. CD5 should be performed on all DLBCL patients, and EBER should be performed in patients with immune suppression related lymphomas, or those who possibly have EBV-related DLBCL the elderly.
    - *MYC* rearrangement by FISH, especially in association with *BCL2* and/or *BCL6* (double or triple hit disease) is associated with very poor outcomes following rituximab + cyclophosphamide + adriamycin + vincristine + prednisone (R-CHOP) therapy, as well as high rates of central nervous system relapse. Such patients under age 70 years should receive more aggressive therapy with a Burkitt lymphoma regimen and possibly stem cell transplantation. Though rare, it is very important to recognize this diagnosis, and therefore, *MYC* rearrangement testing by FISH is required. If *MYC* is rearranged, the case should be followed-up with *BCL2* and *BCL6* rearrangement testing by FISH. The preceding is true for all new diagnoses of DLBCL in patients under 70 years, but especially for patients with:
        a. Atypical morphology (intermediate between DLBCL and Burkitt, usually with a GC cell of origin immunohistochemical [IHC] phenotype)
        b. High proliferation rate by Ki67 >80%, or
        c. DLBCL with aggressive clinical behaviour (as requested by hematologist/oncologist).

      FISH testing may also be performed in select instances at the discretion of the reporting hematopathologist if he/she deems such studies diagnostically useful. Note: *MYC* immunohistochemical studies do not correlate with gene rearrangement status and cannot be used as a surrogate for *MYC* rearrangement in this context.

3. Follicular Lymphoma: Must document grade (1–2, 3a or 3b), because all grade 3b should receive R-CHOP rather than other chemotherapy regimens. Also, if a diffuse pattern is present, this should be specified and a relative proportion noted, as outlined in the WHO Classification.
4. Peripheral T-cell Lymphoma: Cytotoxic T-cell markers (CD8/CD57/Granzyme B) correlate with poor prognosis and should be considered. Notably, however, peripheral T cell lymphomas are not classified on the basis of these phenotypic markers. EBV studies by in situ hybridization (EBER) should be performed in cases where angioimmunoblastic T-cell lymphoma and extranodal T/natural killer (NK) cell lymphoma, nasal type enter in the differential diagnosis.
5. Mantle Cell Lymphoma: IHC for cyclin D1 and/or FISH for t(11;14) is needed to confirm the diagnosis. Poor prognostic features must be mentioned in the report, including blastoid and pleomorphic morphologic variants, as well as proliferation index as measured by Ki67 or Mib-1 (used to calculate Mantle Cell Lymphoma International Prognostic Index [MIPI] score).

<u>Staging</u>

Mandatory Staging Procedures

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination stating Eastern Cooperative Oncology Group (ECOG) Performance Score, B symptoms
- Complete blood count (CBC) and differential
- Serum creatinine, electrolytes, alkaline phosphatase, alanine transaminase (ALT), lactate dehydrogenase (LDH), bilirubin, total protein, albumin, calcium
- Hepatitis B surface antigen (must be done prior to initiating chemo/immunotherapy)
- Erythrocyte sedimentation rate (ESR) (for early-stage Hodgkin lymphoma)
- Beta-2-microglobulin
- Serum protein electrophoresis and quantitative immunoglobulin G (IgG) and immunoglobulin M (IgM) for indolent B-cell lymphomas

- Pregnancy test: if at risk
- Bone marrow aspiration and biopsy (2 cm) with flow cytometry
- Chest X-ray (posteroanterior [PA] and lateral)
- Computed tomography (CT) scan chest/abdomen/pelvis +/- neck

Refer to Table 2 in the original guideline document for selected non-routine tests and required presentation/condition.

Table. Staging System

Stage	Description
Stage I	Single lymph node region (I) or one extralymphatic organ (IE)
Stage II	Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus lymph nodes, same side of the diaphragm (IIE)
Stage III	Lymph node regions on both sides of the diaphragm either alone (III) or with local extra-lymphatic extension (IIIE)
Stage IV	Diffuse involvement of 1 or more extralymphatic organs or sites: • A: No B symptoms • B: At least one of the following: unexplained weight loss >10% baseline within 6 months of staging, unexplained fever >38°C, or drenching night sweats

For treatment planning, patients are divided into 2 groups by stage:

1. Limited stage: Non-bulky stage IA(E) or IIA(E) (≤3 adjacent lymph node regions)
2. Advanced stage:
    - Stage II involving >3 or non-adjacent lymph node regions
    - Or stage III or IV
    - Or B symptoms
    - Or bulky tumour mass (≥10 cm)

Restaging Schedule

1. The following are to be performed prior to each chemotherapy treatment:
    - Clinical parameters: brief history and physical examination, toxicity notation, ECOG status
    - Bloodwork:
        - CBC/differential/platelet
        - Also consider electrolyte panel (EP)/creatinine and liver function tests (LFTs)

2. Requirements for CT scanning of chest/abdomen/pelvis:
    - Routine CT scanning:
        - After 3 months (4 cycles) of therapy and if abnormal, again after completion of all therapy
        - If a residual mass is seen on the CT after completion of all therapy, then consider a positron emission tomography (PET)/CT to determine partial versus complete remission, especially for aggressive histology lymphomas
        - A repeat CT scan should be considered 6 months later; otherwise, no further routine CT scans are required
    - Other requirements for CT scanning:
        - As indicated to investigate clinical signs or symptoms, or abnormal laboratory tests

3. Bone marrow aspirate and biopsy (with sample sent for flow cytometry):
    - Repeat for transplant-eligible patients with aggressive histology lymphomas who otherwise are in complete remission after completion of chemotherapy, if marrow was positive at diagnosis
4. PET/CT imaging:
    - Assessment of residual radiographic or clinical abnormalities of uncertain significance at the time of re-staging following completion of

therapy

Table. PET Result Significance and Treatment Recommendations

Positron emission tomography (PET) Result	Final Response	Treatment Recommendation
Negative	Complete	Observation
Positive	Partial	Consider biopsy, involved field radiation therapy (IFRT), or high dose chemotherapy/autologous stem cell transplantation (HDCT/ASCT) versus observation

Treatment of Non-Hodgkin Lymphomas

Treatment of non-Hodgkin lymphomas is based on histologic subtype, extent of disease, and age of the patient. In the case of discordant (2 separate sites of disease with differing types of lymphoma), composite (1 site of disease with 2 discrete types of lymphoma at that site), or transformed (a second lymphoma developing out of a background of previously known lymphoma) lymphoma, treatment must be directed at the most aggressive phase of the disease. Approaches outlined for aggressive lymphomas are generally applicable to both B- and T-cell types. However, treatments for lymphomas presenting at special sites, poor prognosis lymphomas in younger patients, and lymphomas arising in association with immunodeficiency (human immunodeficiency virus [HIV], post-organ transplant) are outlined in the section titled "Special Problems in Lymphoma Management" below.

Diffuse Large B-cell Lymphoma (DLBCL)

Table. Initial Therapy of DLBCL/Aggressive Lymphomas

Stage	# Risk Factors*	Treatment**
Limited	0–2	• Rituximab + cyclophosphamide + adriamycin + vincristine + prednisone (R-CHOP) x 3 cycles plus involved field radiation therapy (IFRT) (30–35 Gy) for most patients • R-CHOP x 6 without IFRT also an option as well as • If wish to avoid IFRT (especially age <55 years with chest, abdomen or pelvic disease) consider: • If International Prognostic Index (IPI)=0: R-CHOP x 4, then confirm complete remission (CR) by CT or PET/CT • If IPI=1–2: R-CHOP x 6, then confirm CR by computed tomography (CT) or positron emission tomography (PET)/CT
Limited	3–4	R-CHOP x 6 cycles plus IFRT (30–35 Gy)
Advanced***	0–2 or age >65 years	R-CHOP x 6 cycles possibly followed by IFRT (30–35 Gy) to site of prior bulk disease (>10 cm mass) if no CR to chemotherapy
Advanced***	3–5 and age <65 years	Acceptable alternatives: • R-CHOP x 6, then high-dose therapy/autologous stem cell transplantation (ASCT) if no CR or relapse, or • R-CHOP induction then high-dose chemotherapy/stem cell transplantation in first remission, or • Rituximab + cyclophosphamide + adriamycin + vincristine + etoposide + prednisone (R-CHOEP)-14 x 6 cycles • IFRT (30–35 Gy) to site of prior bulk disease (>10 cm mass) if no CR to chemotherapy • Consider need for central nervous system (CNS) prophylaxis with high-dose intravenous (IV) methotrexate as described later in guidelines (with R-CHOEP cycles 2, 4, and 6, give methotrexate on day 15 and start next cycle on day 21)

*IPI Risk Factors for Limited Stage: increased LDH, stage II, ECOG performance status 2–4, age >60 years.

*IPI Risk Factors for Advanced Stage: increased LDH, stage III/IV, >1 extranodal site, ECOG performance status 2–4, age >60 years.

**R-CEOP should be used for DLBCL patients who have prior cardiac disease and reduced left ventricular ejection fraction. As presented by the BC Cancer Agency at the American Society of Hematology (ASH) 2009 Meeting (abstract 408), R-CEOP (etoposide 50 mg/m^2 IV day 1 and 100 mg/m^2 po days 2–3) resulted in a 5 year time to progression (TTP) of 57% for 81 patients with DLBCL.

***For patients >age 60 years, 3–7 days of prednisone 100 mg/day pre-R-CHOP as well as granulocyte-colony stimulating factor (G-CSF) prophylaxis is recommended to decrease toxicity.

Due to the lack of proven benefit, intrathecal chemotherapy cannot be recommended even in high-risk situations where the risk of central nervous system (CNS) relapse is approximately 10% or higher.

Recommendations for Treatment

For DLBCL with associated high-risk features for relapse in the CNS, including all of: elevated LDH, ECOG=2–4 and >1 extranodal site of involvement at diagnosis, CNS prophylaxis should involve high-dose intravenous (IV) methotrexate 3.5 g/m^2 x 3 doses mid-cycle (~day 15) of R-CHOP or rituximab + cyclophosphamide + adriamycin + vincristine + etoposide + prednisone (R-CHOEP) cycles 2, 4, and 6. For other high-risk presentations not fulfilling the 3 risk factors stated above (e.g., paranasal sinus, epidural, or testicular presentations), CNS prophylaxis should involve high-dose IV methotrexate 3.5 g/m^2 every 14–28 days x 2–3 doses after completion of all 6 cycles of R-CHOP. The overall chance of cure and patient co-morbidities should be considered before proceeding with methotrexate. For example, high-risk International Prognostic Index (IPI) DLBCL in elderly patients over age 70 years is associated with low progression-free survival rates, and poor tolerance of methotrexate, so CNS prophylaxis is probably not appropriate.

Treatment of Relapsed DLBCL

All patients younger than 65 to 70 years of age who experience disease persistence or progression after initial R-CHOP chemotherapy should be considered for high-dose salvage therapy with autologous stem cell transplantation (ASCT). These patients should be referred to the bone marrow transplant (BMT) clinic as soon as possible, or a transplant physician should be contacted directly to discuss management decisions. See the original guideline document for additional information on suggested management.

Selected patients with isolated CNS relapse/progression following complete response to R-CHOP-type induction therapy may be candidates for aggressive therapy as outlined in Appendix A, subheading VIII, section C (see the original guideline document). Unfortunately, most patients with secondary CNS lymphoma also have evidence of systemic disease progression, and experience poor response to salvage therapy, including high-dose methotrexate/cytarabine-based regimens. These patients are best managed with palliative intent, including possible use of intrathecal chemotherapy or palliative cranial radiotherapy.

Treatment of Special DLBCL Entities

1. Intermediate between DLBCL and Burkitt Lymphoma:
    - *MYC* normal (negative), or *MYC* mutated but age >70 years: R-CHOP x 6 cycles
    - *MYC* positive (mutated) and age <70 years: rituximab + cyclophosphamide + vincristine + adriamycin + methotrexate (R-CODOX-M)/ifosfamide + mesna + etoposide + cytarabine (IVAC)
    - *MYC* positive and other adverse factors such as *BCL2*+ (double hit) or involved marrow: consider R-CODOX-M/IVAC + HDCT/ASCT
2. Intermediate between DLBCL and Hodgkin Lymphoma:
    - R-CHOP x 6 cycles for most patients
    - Consider R-CHOEP x 6 cycles if high-risk factors are present (i.e., IPI=3–5 or IPS=3–7)

Follicular Lymphoma

Throughout the following suggested treatment approach, 3 over-riding principles should be considered:

1. These are guidelines only. This disease often carries a long, incurable, remitting/relapsing natural history and, therefore, several treatment approaches are reasonable.
2. The mere presence of disease does not alone imply the need for treatment.
3. If therapy is required for predominantly localized disease, involved field radiation therapy (IFRT) should be considered in lieu of systemic

pharmacological treatment as long as the radiotherapy can be done with minimal early or delayed side-effects (e.g., xerostomia, severe nausea/vomiting) and without eliminating future treatment options (e.g., should not radiate ≥25% bone marrow). Figure 2 in the original guideline document outlines the treatment algorithm for follicular lymphoma.

Initial Therapy of Stage IA and Contiguous Stage IIA

IFRT 24 Gy/12–30 Gy/20 fractions is recommended for newly-diagnosed patients with stage IA or contiguous non-bulky stage IIA follicular lymphoma, even if the patient is asymptomatic.

Initial Therapy of Advanced Stage Disease (Stage III/IV, B symptoms, or Bulky Stage I/II)

Indications for systemic therapy (usually stage III/IV or bulky stage I/II) include:

- Patient symptoms (fever, night sweats, weight loss, malaise, pain, nausea)
- Significant lymphadenopathy (>7 cm mass, ≥3 sites and ≥3 cm, rapidly progressive)
- Splenomegaly ≥6 cm below costal margin, or hypersplenism, or pain
- Impending organ compromise (compression, pleural/pericardial effusions, ascites)
- Cytopenias secondary to bone marrow infiltration
- Patient preference because of anxiety and poor quality of life without treatment

For patients who do not have any of the above indications for therapy, the recommended approach is to observe with (or arrange) follow-up clinical assessments every 3 to 6 months ("watchful waiting").

For grades 1, 2, 3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6 cycles of bendamustine-rituximab (B-R) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375 mg/m^2 IV single dose every 3 months for total of 8 doses). In patients with previously untreated indolent lymphoma, B-R can be considered as a preferred first-line treatment approach to R-CHOP because of increased progression-free survival and fewer side-effects. Patients who have limited life-expectancy from co-morbid illness, or who do not want IV therapy, may be treated with oral chlorambucil or fludarabine monotherapy.

For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

Therapy of Relapsed Disease

Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including:

- Patient factors: Age, co-morbidity, symptoms, short- vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (response rate [RR], progression-free survival [PFS], overall survival [OS])
- Disease factors: Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval)

See the original guideline for additional information concerning management of recurrent follicular lymphoma, including suggested chemotherapy regimens and radiotherapy.

Indolent Lymphomas (Excluding Follicular Histology)

Indolent lymphomas should generally be treated similarly to follicular grade 1–2 lymphomas.

Table. Treatment of Indolent Lymphomas

Stage	Treatment
Limited	Involved field radiation therapy (IFRT) (24 Gy/12–30 Gy/20)
Advanced	Asymptomatic: Observation until treatment indication Symptomatic: • Majority should receive bendamustine-rituximab (B-R), then rituximab maintenance

Stage	Treatment
	• Alternatives in special situations include IFRT, fludarabine, or chlorambucil

Recurrent CD20+ indolent B-cell lymphomas should be considered for rituximab therapy alone (375 mg/m^2 weekly x 4) or rituximab plus chemotherapy (B-R, R-fludarabine, R-fludarabine + cyclophosphamide [FC], R-fludarabine + mitoxantrone + dexamethasone [FND], R-CVP), or chemotherapy alone (chlorambucil; fludarabine; etoposide; cyclophosphamide, etoposide, procarbazine, prednisone [CEPP]; gemcitabine, dexamethasone, and cisplatin [GDP]; FND; cisplatin + etoposide + cyclophosphamide [PEC]; or mitomycin C, etoposide, cisplatin [MEP]). Patients less than 70 years of age without serious co-morbid disease, and who respond to salvage therapy could be considered for high-dose chemotherapy and autologous or allogeneic stem cell transplantation.

Lymphoplasmacytic Lymphoma (LPL)

Diagnostic Criteria for Waldenström Macroglobulinemia (WM)

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation
- Intertrabecular pattern of bone marrow infiltration
- LPL immunophenotype:
    - Surface IgM+ CD5- CD10- CD19+ CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138-

Diagnostic Approach to Confirm a Suspected Case of WM

1. Serum protein electrophoresis with immunofixation: to characterize the type of light and heavy chains
2. 24-hour urine for protein electrophoresis: 40% to 80% have detectable Bence Jones proteinuria
3. Serum B2-microglobulin: for prognostic evaluation
4. Bone marrow biopsy: intratrabecular monoclonal lymphoplasmacytic infiltrate, ranging from predominantly lymphocytic to lymphoplasmacytic to overt plasma cells
5. CT of the abdomen and pelvis: to detect organomegaly and lymphadenopathy (skeletal surveys and bone scans are not necessary in absence of symptoms)
6. Blood or plasma viscosity: if signs and symptoms of hyperviscosity syndrome (HVS) or IgM >50 g/L
7. Direct antiglobulin test and cold agglutinin titre if positive
8. Cryoglobulins

IgM Monoclonal Protein Response Assessment in WM

Serum IgM monoclonal protein should be measured by serum protein electrophoresis. The use of nephelometry to determine total serum IgM should be discouraged because this method is unreliable, especially when the levels of monoclonal protein are high. The presence of cryoglobulin or cold agglutinin may affect determination of IgM; therefore, testing of cryoglobulin and cold agglutinin at baseline should be considered, and if present, serum samples should be reevaluated at 37°C to ensure accurate and consistent determination of the monoclonal protein levels.

HVS in LPL

Symptoms and signs of hyperviscosity include spontaneous bleeding, neurological symptoms and retinopathy. Patients with HVS have an expanded plasma volume and cardiac failure may also occur. In patients with WM the actual plasma volume may exceed that calculated and a 1–1.5 volume exchange is therefore advisable.

General Treatment Guidelines for LPL/WM

The usual indications for starting patients with LPL/WM on active therapy consist of clinical evidence of adverse effects of the paraprotein (HVS with neurological or ocular disturbance, peripheral neuropathy, amyloidosis, symptomatic cryoglobulinemia), blood cytopenias (hemoglobin [Hb] <100, platelets <100), progression to high-grade lymphoma, significant adenopathy or organomegaly, or constitutional symptoms.

- *Plasmapheresis*: 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, are advised for the treatment of HVS in WM, followed by chemotherapy to prevent paraprotein re-accumulation. In patients who are drug-resistant, plasmapheresis may be indicated for long-term management. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.
- *Chemotherapy*: The most common initial chemotherapy for LPL is B-R followed by rituximab maintenance, similar to other indolent B-cell lymphomas. Alkylating agent-based therapy or purine analogues are also reasonable for the initial and subsequent treatment of WM, especially for older patients with significant co-morbid illnesses. There is no consensus on the duration of treatment with cladribine or

fludarabine, or on which purine analogue is superior. While fludarabine is more active than cyclophosphamide + adriamycin + prednisone (CAP) as salvage therapy, neither of these therapies has been shown to offer survival benefit over another. Rituximab is active in the treatment of WM but associated with the risk of transient exacerbation of clinical effects of the disease and should be used with caution in patients with symptoms of hyperviscosity and/or IgM levels >40 g/L. ASCT is used with increasing frequency for LPL, and as such, purine analogue therapy and chlorambucil should be avoided as initial therapy for transplant-eligible patients to prevent stem cell damage and decrease the risk of blood mobilization failure in the future.

- Thalidomide is of potential use in the treatment of patients who have previously received alkylating agents, purine analogues and antibody therapy. Other agents are currently only recommended in the context of clinical trials.
- High-dose therapy supported by ASCT has a role in the management of selected patients with WM who have chemosensitive primary induction failure or relapsed disease (preferably first relapse). Autologous stem cell collection is often not possible for patients who have received more than 4 months of prior chlorambucil or purine analogue (fludarabine or 2-CDA) therapy. As with other indolent lymphomas, ASCT should be considered at second relapse, before the disease develops absolute chemoresistance.

Special Lymphomas

These diagnoses sometimes constitute an oncologic emergency. Treatment may require intensive high-dose chemotherapy with CNS prophylaxis, and may need to begin within 48 hours, whether staging is complete or not. Patients should be seen for consultation at a major referral centre and may require complicated high-dose chemotherapy regimens. Acceptable treatment approaches for some of the entities (mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's and high-grade B-cell Burkitt's-like lymphoma) are outlined in the original guideline document.

Special Problems in Lymphoma Management

Gastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

For complete staging evaluation, patients with gastric MALT lymphoma require gastroscopy and multiple large deep biopsies stained for *Helicobacter pylori*. Stage IAE low-grade gastric MALT should be treated with omeprazole 20 mg twice daily, clarithromycin 500 mg twice daily and either metronidazole 500 mg twice daily or amoxicillin 1,000 mg twice daily for 1 week, or an equally effective regimen such as lansoprazole + clarithromycin + amoxicillin (Hp-PAC). After treatment with antibiotics, patients should undergo repeat gastroscopy at 3 months, then every 6 months for 2 years, then annually for 3 years. Biopsies should be taken for lymphoma and *H pylori* each time. One re-treatment should be tried if *H pylori* persists. MALT lymphoma may slowly regress over 12 to 18 months after *H pylori* eradication. If lymphoma recurs or persists more than 12 to 18 months after eradication of *H pylori*, the patient should receive upper abdominal irradiation (30 Gy/20 fractions with POP if anatomy permits, otherwise 4–5 field plan with superior portion anteroposterior (AP)/PA and inferior portion AP, R lateral and L lateral). Patients could also be considered for IFRT rather than *H pylori* therapy if the tumour is associated with t(11;18), nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), or nuclear bcl-10 expression. Stage IIAE or greater gastric MALT should be managed as advanced low-grade lymphoma plus eradication of *H pylori* with antibiotics. Other histologies of gastric lymphoma should be managed as per the sections on aggressive lymphomas or follicular lymphomas found in the original guideline document.

Testicular Lymphoma

In contrast to other patients with localized large B-cell lymphoma, patients with stage IAE or IIAE testicular lymphoma are cured less than 50% of the time using brief chemotherapy and irradiation. Thus, the recommended treatment for all stages of testicular lymphoma is a full course of chemotherapy (R-CHOP x 6 cycles). An additional problem often seen in these patients is relapse in the opposite testicle. This can be prevented by scrotal irradiation (25–30 Gy/10–15 fractions). Finally, these patients are at high risk for CNS relapse. Although some experts recommend prophylactic intrathecal chemotherapy, especially for stages 3–4 disease, this has not been proven effective. Unfortunately, many of the CNS relapses occur within the brain parenchyma, and are not prevented by intrathecal chemotherapy. For this reason, CNS prophylaxis should involve high-dose IV methotrexate 3.5 g/m^2 every 14 to 28 days x 2–3 doses after completion of all 6 cycles of R-CHOP.

Primary CNS Lymphoma (PCNSL)

Diagnosis of PCNSL is based on a biopsy of the brain lesion, or pathological examination of a vitrectomy or cerebrospinal fluid (CSF) specimen. A bone marrow biopsy and CT scan of the chest, abdomen, and pelvis is required to rule out systemic disease. Required staging tests include ophthalmologic slit lamp exam and CSF cytology (only if lumbar puncture is not contraindicated because of intracranial hypertension and midline shift). Human immunodeficiency virus (HIV) serology should also be obtained. If initial CSF cytology is obtained while the patient is receiving corticosteroids and is negative, it should be obtained 1 month after completing all therapy, after corticosteroids have been discontinued.

Treatment of PCNSL involves induction chemotherapy based upon high-dose methotrexate 3.5–5 g/m^2 every 2 weeks for 4–5 doses. Intrathecal methotrexate has not been shown to be beneficial if high-dose methotrexate is used. It is recommended to use high-dose methotrexate and cytarabine during induction therapy for PCNSL.

For a detailed description of recommended PCNSL treatment regimens, please refer to Appendix A, subheading VIII, sections A and B in the original guideline document.

For palliative therapy, doses of cranial radiotherapy should be 30 Gy in 10–20 fractions.

Eye Lymphoma

Orbital or Peri-orbital Lymphoma

Peri-orbital lymphoma of the bony orbit or the soft tissues in and around the orbit but outside of the globe and optic nerve should be managed as indicated in the earlier sections on aggressive lymphomas, marginal zone lymphomas or follicular lymphoma, as appropriate for the type and stage of the lymphoma. Approximately 40% of such patients have advanced disease discovered when carefully staged. In general, 25–30 Gy/20 fractions radiotherapy to whole orbit/peri-orbital tissue is recommended for indolent peri-orbital lymphomas.

Conjunctival Lymphoma

Lymphoma involving the conjunctiva but not the structures within the globe or the optic nerve is usually of low grade and should be treated with 25–30 Gy/20 fractions of radiotherapy. Doses, fields, and shielding specifically modified for treatment of the eye are necessary to minimize long-term complications such as xerophthalmia or cataract formation.

Intra-ocular and Optic Nerve Lymphoma

- Lymphoma involving the vitreous, retina or other structures within the optic nerve or globe is usually of large cell type and is equivalent to PCNSL. Bilateral involvement is common. Evaluation and management should be the same as for PCNSL. Acceptable treatment involves induction chemotherapy with high-dose methotrexate and high-dose cytarabine as described for PCNSL in Appendix A of the original guideline document
- Lymphoma involving the uveal structures (choroid) is a rare presentation of lymphoma, and is usually of indolent type. This disease is best managed with treatment appropriate for stage and local extent of disease

Cutaneous Lymphoma

Cutaneous lymphomas should be treated according to histological type and site of presentation. In general, B-cell lymphomas are localized and T-cell lymphomas tend to be disseminated. Diagnosis requires full thickness punch or excisional skin biopsy of lesion, and no involved sites other than skin for 6 months after diagnosis. Staging tests are required as described in the staging section above.

Cutaneous T-cell Lymphomas (CTCL)

Mycosis Fungoides (50% of cutaneous lymphoma)

Refer to Table 7 in the original guideline document for staging of mycosis fungoides.

Table. Treatment of Mycosis Fungoides

Treatment	Details
Topical	• Stages I–IIA usually respond to topical corticosteroids, nitrogen mustard or carmustine (BCNU). • Approximately 50% experience a CR.
Psoralen and ultraviolet (UV) radiation	• If topical treatment fails, then psoralen and ultraviolet A radiation (PUVA) may be tried. PUVA is usually given 2–3 times/week initially, then less frequently as maintenance therapy. • Most patients require long-term treatment.
Total skin electron beam irradiation	• Electron beam radiation only penetrates the dermis, allowing treatment of cutaneous T-cell lymphoma (CTCL) without toxicity to underlying tissue. • Total skin electron beam irradiation is carried out mainly at the Credit Valley Hospital, Mississauga (Glenn Jones). • Early stage patients may experience extremely long disease-free survival with this approach.

Treatment	Details
Conventional radiation	• Multiple tumours within the skin often require systemic treatments, but local nodules often respond well to localized external beam radiation.
Interferon-alfa	• First-line systemic treatment often is interferon alfa-2a or b, in doses up to 10 million units three times weekly. • Prolonged treatment is often required and tolerance is poor due to flu-like symptoms, fatigue, and depression.
Chemotherapy	• Usual initial choices of chemotherapy are chlorambucil, cyclophosphamide, or methotrexate. • If multiple lymph nodes or visceral organs are involved, often cyclophosphamide + adriamycin + vincristine + prednisone (CHOP) is used. • Purine analogues such as deoxycoformycin, fludarabine, and cladribine are usually used for patients who have progressive disease after alkylator-based chemotherapy. • Another drug with activity in this disease is gemcitabine.
Extracorporeal photophoresis	• The patient is given a psoralen derivative and then undergoes leucopheresis. The blood is passed through an aperture that exposes it to UV light, activating psoralen in the lymphoma cells, killing the cells. The dead cells may then act as better antigens and generate an immune response to the CTCL. It is another option for patients who have failed standard therapies stated above.
DAB389IL-2 (Denileukin Diftitox - Ontak)	• This is an interleukin (IL)-2 derivative fused to a portion of diphtheria toxin. CTCL express the IL-2 receptor (CD25) with high density and are sensitive to this compound. The agent is given daily x 5 days, every 3 weeks. Approximately 30% of heavily pre-treated patients respond to this therapy, but toxicity can be severe with capillary leak syndromes, hypotension, rash, and chest pain. • Available in Canada only through emergency drug release, and rarely used.
Bexarotene	• This is an anti-tumour retinoid available in capsules and as a topical gel. • Response rates of >50% have been reported, even for heavily pre-treated, advanced stage patients. • It can produce hyperlipidemia, hypercholesterolemia, hypothyroidism, asthenia, leucopenia, headache, diarrhea, and skin flaking. It is mainly used for patients who have failed more standard treatment approaches. • The initial dose is 300 mg/m^2/day.
Novel therapies	• IL-12 and Campath (anti-CD52 monoclonal antibody) have reported activity against CTCL and may prove to be useful agents for this disease.

Other Cutaneous T-cell Lymphomas (25% of cutaneous lymphomas)

- Indolent:
  - 85%–100% survival rate
  - CD30+ localized T-cell - treat with IFRT 30–35 Gy
- Intermediate:
  - 50%–60% survival rate
  - Pleomorphic - treat with cyclophosphamide + adriamycin + vincristine + prednisone (CHOP) x 3 cycles plus IFRT 30–35 Gy
  - Small/medium sized peripheral T-cell lymphoma - treat with CHOP x 3 cycles plus IFRT 30–35 Gy
- Aggressive:
  - 10%–20% survival rate
  - CD30-localized T-cell - treat with CHOP x 6 cycles plus IFRT 30–35 Gy
  - Subcutaneous panniculitic (often die of sepsis, 30–40 years of age) - treat with CHOP x 6 cycles plus IFRT 30–35 Gy
- Variable:

- Angiocentric T/NK - treat with CHOP x 3–6 cycles plus IFRT 30 Gy/10 or 45 Gy/25
- Angioimmunoblastic - treat with CHOP x 3–6 cycles plus IFRT
- Intravascular T-cell - treat with CHOP x 3–6 cycles plus IFRT

Cutaneous B-cell Lymphomas (25% of cutaneous lymphomas)

- Indolent (90%):
  - 90%–95% survival rate
  - Follicle centre of head and neck, trunk (including follicular or diffuse large cell) - treat with IFRT 30 Gy
  - Marginal zone (often extremities) - treat with IFRT 30 Gy
  - Cutaneous plasmacytic - treat with IFRT 30 Gy
- Intermediate:
  - 50%–60% survival rate
  - Large B-cell lymphoma of the leg - treat with R-CHOP x 6 cycles and consider IFRT 30–35 Gy if localized
- Variable:
  - Intravascular B-cell (often ulcer or painful plaque/patch) - treat with R-CHOP x 6 cycles and consider IFRT 30–35 Gy if localized

Aggressive T-Cell Lymphomas

NK/T-cell Lymphoma, Nasal Type

NK/T-cell lymphoma, nasal type is a rare and aggressive extranodal neoplasm that almost exclusively affects Asian and South American adults in the fifth decade of life, with a male:female ratio of approximately 3:1. It typically arises in the nasal cavity or surrounding structures, such as the sinuses, palate, nasopharynx, tonsils, hypopharynx, and larynx. While the pathogenesis of NK/T-cell lymphoma, nasal type is not well understood, EBV is implicated in almost all cases. Approximately 25% of cases show a p53 mutation; in addition, p21 over-expression is also frequent in nasal NK/T-cell lymphoma, and seems to be independent of p53 gene status.

Hematopathological evaluation of a biopsy specimen from the site of involvement is the basis for diagnosis of nasal NK/T-cell lymphoma. The recommended immunohistochemistry panel includes:

- B-cell: CD20
- T-lineage antigens: CD2, CD7, CD8, CD4, CD5, CD3
- NK lineage markers: CD56
- Ki-67
- *In situ* hybridization for EBV-encoded ribonucleic acid (RNA) (EBER)

For patients with early-stage nasal NK/T-cell lymphoma, early or upfront radiotherapy (intensive regimens such as a total dose 50–54 Gy, or an accelerated dose of 30 Gy/10 fractions) plays an essential role in therapy, and has been associated with higher overall survival and complete response rates compared to chemotherapy alone. However, radiotherapy alone is associated with high relapse rates. Combined modality therapy is recommended.

For patients with stage III–IV disease, complete remission rates are less than 15%, and the median overall survival is approximately 4 months. The recommended options for therapy include either enrollment in a clinical trial or treatment with an L-asparaginase-based combination chemotherapy regimen. Allogeneic or autologous SCT could also be considered in patients with disseminated disease that is responsive to chemotherapy, although data is limited.

Peripheral T-cell Lymphomas (PTCL)

With the exception of anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma, CHOP chemotherapy cures less than 30% of patients with PTCL. Options that may be associated with higher cure rates include CHOP x 4–6 cycles followed by HDCT/ASCT in responding patients or intensification of CHOP with etoposide (CHOEP).

For PTCL patients who relapse following CHOP-type induction and respond to salvage therapy, ASCT should be recommended, as several studies report similar ASCT outcomes to those seen with relapsed DLBCL.

Summary of treatment recommendations for PTCL:

1. Anaplastic large cell lymphoma, ALK positive: CHOP x 6 cycles
2. NK/T-cell lymphoma, nasal type:

- Recommendation for stage I–II NK/T-cell lymphoma: IFRT as initial therapy (either 30 Gy/10 fractions IFRT or concurrent 40–50 Gy IFRT+ weekly cisplatin 30 mg/m^2) then follow IFRT with etoposide + ifosfamide + cisplatin + dexamethasone (VIPD) x 3 cycles (etoposide 100 mg/m^2 days 1–3 + ifosfamide 1.2 g/m^2 days 1–3 + cisplatin 33 mg/m^2 days 1–3 + dexamethasone 40 mg days 1–4)
- If IFRT must be delayed for 2 or more weeks after diagnosis due to scheduling issues, then days 1–4 of GDP could be administered while waiting for IFRT

3. All other subtypes of PTCL:
    - <60 years of age with IPI=0–2: CHOEP x 6 cycles
    - <60 years of age with IPI=3–5: CHOEP x 4 cycles, then mobilize stem cells with high-dose methotrexate (MTX) 3.5 g/m^2 IV day 1 and cytarabine 3 g/m^2 IV days 9–10, G-CSF 480–600 mg subcutaneously (SC) daily days 16–21 followed by apheresis days 22–23, then HDCT/ASCT
    - >60 years of age: CHOP or CEOP x 6 cycles +/- HDCT/ASCT, or cyclophosphamide + etoposide + methotrexate + dexamethasone + leucovorin + G-CSF (CMED)

Acquired Immunodeficiency Syndrome (AIDS)-Related Lymphomas

In general, the treatment of AIDS-related lymphoma should be the same as for non-AIDS related lymphoma if the AIDS does not otherwise compromise the patient's performance status and he/she is free of coincident serious opportunistic infection. Highly active antiretroviral therapy (HAART) should be given with CHOP chemotherapy. R-CHOP results in the highest rates of disease-free survival, but may also increase the risk of infectious complications and treatment-related mortality in patients with CD4 counts below 50.

Post-transplant Lymphoproliferative Disease (PTLD)

PTLD may have a variety of histological presentations, and all diagnoses require review by an expert hematopathologist. Treatment of PTLD requires close collaboration between the organ transplant team and lymphoma team. Transplant patients receiving immunosuppressant medications tolerate chemotherapy poorly, often developing profound and prolonged pancytopenia.

General treatment principles include:

- The immunosuppression should be reduced to the absolute minimum, zero if possible, even if that requires endangering the grafted organ. Some lymphomas, especially polymorphic PTLDs that developed within the first 2 years of organ transplantation, will spontaneously regress if the immunosuppression can be sufficiently reduced
- If reduction of immunosuppression fails to control the lymphoma, a member of the core group should be consulted to determine if rituximab alone, R-chemotherapy, radiotherapy, interferon, or novel experimental treatment would be of use

Hodgkin Lymphoma

Pathologic Classification

The histological sub-classification of Hodgkin lymphoma is based on the light microscopic hematoxylin and eosin (H&E) interpretation. If problems with differential diagnosis arise, staining for CD15, CD30, T-cell and B-cell panels and epithelial membrane antigen (EMA) may be helpful. For lymphocyte predominant Hodgkin lymphoma, CD20, CD45, +/- CD57 are recommended.

Refer to Table 9 in the original guideline document for the WHO classification of histologic subtypes of Hodgkin lymphoma.

Staging

Mandatory staging procedures include:

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination (B symptoms, Etoh intolerance, pruritis, fatigue, ECOG performance score, examination of nodes, Waldeyer's ring, spleen, liver, skin)
- CBC and differential, creatinine, electrolytes, alkaline phosphatase, ALT, LDH, bilirubin, total protein, albumin, calcium
- ESR
- Bone marrow aspiration and biopsy (2 cm core preferable) for stage IIB–IV or cytopenias (*Note: flow cytometry on the marrow aspirate does not add useful information and should not be done*)
- Chest x-ray (PA and lateral)
- CT scan of the chest, abdomen, and pelvis

In addition, it may be useful to perform the following procedures in selected cases:

- PET scan, especially for clinical stage I–IIA by standard CT imaging
- Ear, nose, and throat (ENT) exam for clinical stage I–IIA upper cervical (above hyoid) nodal disease
- Pregnancy test, if at risk
- Fertility and/or psychosocial counseling
- Pneumococcal, flu, meningococcal vaccines if splenectomy or splenic radiotherapy is contemplated
- Semen cryopreservation if chemotherapy or pelvic radiotherapy is contemplated
- Oophoropexy if premenopausal and pelvic radiotherapy is contemplated
- HIV: risk factors, unusual disease presentations

Primary Treatment of Classical Hodgkin Lymphoma

General Principles

For treatment planning, clinical stage (CS) and histologic type should be taken into account. The following guidelines apply to adults between the ages of 18 and 65 years. Different principles may apply to pediatric and elderly patients.

Table. Treatment Planning for Hodgkin Lymphoma

Clinical Stage (CS)		Treatment Regimen
CS I–II, all histologies *Unfavourable risk factors for non-bulky CS I–IIA include any of: Erythrocyte sedimentation rate (ESR) >50, or ESR >30 with B-symptoms, ≥3 sites or extranodal disease*	Favourable risk, nonbulky CS I–II	• Adriamycin + bleomycin + vinblastine + dacarbazine (ABVD) x 2 cycles, then IFRT (20 Gy) is standard for most patients** • For patients who wish to avoid IFRT (especially <55 years old with disease in mediastinum or abdomen) • ABVD x 2 cycles then positron emission tomography/computed tomography (PET/CT) • If PET negative, then further ABVD x 2 cycles • If PET positive, then IFRT • For patients who refuse chemotherapy: extended field/STNI • For patients with non-bulky nodular sclerosis CS IA with high neck or epitrochlear nodes <3 cm: consider IFRT alone • For peripheral CS IA lymphocyte predominant Hodgkin lymphoma: IFRT alone
	Unfavourable risk, nonbulky CS I–II (any unfavourable risk factor)	• ABVD x 4 cycles, then IFRT (30 Gy) • Alternative for patients with significant B symptoms or extranodal extension: ABVD x 6 cycles
	Bulky* CS I–II (mass >10 cm or >1/3 maximal transthoracic diameter on chest x-ray)	• ABVD x 6 cycles, then IFRT (30 Gy) to prior bulk site
CS III and IV, all histologies	Non-bulky disease	• ABVD x 6-8 cycles if IPS 0–2 or age >60 yrs or patient declines bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine +

Clinical Stage (CS)		Treatment Regimen
		prednisone (BEACOPP) due to infertility risk*** or other toxicities • BEACOPP if <60 years old with 3–7 IPS factors • Escalated BEACOPP x 6 cycles • Consider IFRT if there is a localized PET positive residual mass
	Bulky disease	• ABVD or BEACOPP as above, then IFRT to site of prior bulk • Alternative: Patients who wish to avoid IFRT (especially aged <55 years with disease in mediastinum or abdomen) should consider PET/CT after chemotherapy, and IFRT only if there is a localized PET positive mass >2.5cm

IFRT, involved field radiation therapy (20–30 Gy/20 fractions); STNI, subtotal nodal irradiation (30 Gy/20 fractions mantle + 25 Gy/20 fractions to spleen, celiac, para-aortics).

*Bulky disease: MTD (maximum transthoracic diameter) = mediastinal mass width/maximum intrathoracic width >1/3, or any mass >10 cm.

**For ABVD: Perform pulmonary function test at baseline and after cycles 3 and 5; omit bleomycin if ≥25% decrease in diffusing capacity of the lung for carbon monoxide (DLCO) or forced vital capacity (FVC); decrease bleomycin dose by 50% if 10%–24% decrease in DLCO or FVC.

***International Prognostic Score: Age ≥45 years, Male, Stage IV, Albumin <40 g/L, Hb <105 g/L, white blood count (WBC) ≥15 x 10^9/L, Leukocyte <0.6 x 10^9/L or <8% WBC.

Indications for the use of escalated BEACOPP in Alberta include all of the following:

- Stage 3–4
- IPS score 3–7
- Age <60 years
- Karnofsky Performance Status (KPS) score ≥70
- HIV negative, no other co-morbidities
- Patients must be made aware of fertility implications, and consent to proceed

Management of Recurrent Hodgkin Lymphoma

Similar to the initial workup, recurrent disease should involve a bone marrow biopsy and re-staging.

Initial Relapse

- If initial therapy was radiotherapy alone: adriamycin + bleomycin + vinblastine + dacarbazine (ABVD) x 6–8 cycles ± IFRT (20–30 Gy) if localized relapse outside of the original radiotherapy field
- If first-line therapy included chemotherapy (any disease-free interval): Re-induction chemotherapy with GDP or dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra (DICEP) then high dose therapy and ASCT ± IFRT 20–30 Gy to prior bulk site at relapse

Second or Subsequent Relapse

- IFRT if localized relapse in previously non-irradiated site
- Palliative chemotherapy for symptomatic patients (GDP, cyclophosphamide + vincristine + procarbazine + prednisone [COPP], chlorambucil + vinblastine + procarbazine + prednisone [ChlVPP], CEPP, vinblastine)
- Allogeneic SCT only in motivated healthy patients <60 years old with chemosensitive disease, ECOG 0–2, and time to relapse of >1 year following high-dose therapy and ASCT

Refer to Figure 3 in the original guideline document for the treatment algorithm for Hodgkin lymphoma.

Nodular Lymphocyte Predominant Hodgkin Lymphoma

This rare subtype comprises approximately 5% of all Hodgkin lymphomas and is recognized to have a very indolent nature, as well as excellent survival. Many patients present with limited stage disease and, given the excellent prognosis, many centres advocate less intensive therapy than for classical Hodgkin, including surgery alone, watch-and-wait, or isolated IFRT. A recent retrospective study suggests that treatment with combination therapy (with ABVD x 2 cycles followed by IFRT) may be superior to IFRT alone. Given a lack of quality evidence to suggest that nodular lymphocyte predominant Hodgkin lymphoma should be treated differently from classical Hodgkin lymphoma, most patients should be treated similar to the previous guidelines for classical Hodgkin lymphoma.

HDCT and Hematopoietic Stem Cell Transplantation for Lymphoma

For detailed information on hematopoietic stem cell transplantation in patients with hematological malignancies, please refer to the Alberta Bone Marrow and Blood Cell Transplant Standard Practice Manual at http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-bmt-manual.pdf .

Summary of Recommendations

Eligibility

- Patient: age ≤70 years, ECOG 0–2, adequate organ function, no active infections
  - HIV not contraindication if CD4 >100 and meet other eligibility criteria
- Lymphoma: chemosensitive: partial response (PR) or better to last chemotherapy
  - No active secondary CNS disease (eligible if CNS in remission)

HDCT Regimen for Autologous Stem Cell Transplantation

- Indolent (follicular, Mantle cell, small lymphocytic lymphoma [SLL]/chronic lymphocytic leukemia [CLL], marginal zone lymphoma [MZL], LPL): melphalan 180 mg/m^2 + TBI 5 Gy
- Aggressive systemic non-Hodgkin lymphoma (DLBCL, PTCL): rituximab + carmustine + etoposide + cytarabine + melphalan (R-BEAM)
- Hodgkin lymphoma: melphalan 200 mg/m^2
- Primary CNS lymphoma: thiotepa 600 mg/m^2 + busulfan 9.6 mg/kg
- Secondary CNS lymphoma: (R-TBM) thiotepa 500 mg/m^2 + busulfan 9.6 mg/kg + melphalan 100 mg/m^2

HDCT Regimen for Allogeneic Stem Cell Transplantation

- Majority of patients: fludarabine 250 mg/m^2 + busulfan 12.8 mg/kg + antithymocyte globulin (ATG)
- Reduced intensity: fludarabine 120 mg/m^2 + melphalan 140 mg/m^2 + ATG
  - Co-morbidities (liver, lung, nervous system), prior busulfan
  - Slowly progressive, non-bulky lymphoma

Indications for HDCT and Autologous Stem Cell Transplantation

1. Indolent non-Hodgkin lymphoma
   - Follicular, marginal zone, small lymphocytic, lymphoplasmacytic lymphoma
     - Chemosensitive first or second chemotherapy failure
   - Mantle cell lymphoma (especially low or low-intermediate risk MIPI score)
     - First partial remission (PR) or first CR
2. Aggressive non-Hodgkin lymphoma
   - Part of first salvage therapy for chemosensitive first relapse or first remission-induction failure
   - Part of initial therapy for high/intermediate high-risk patients (AAIPI=2–3 or IPI=3–5)
     - First CR following completion of full induction (i.e., R-CHOP x 6)
     - High-dose sequential remission-induction therapy
3. Hodgkin lymphoma
   - First chemotherapy failure (relapse or 1^0 refractory)

Indications for HDCT and Allogeneic Stem Cell Transplantation for Lymphoma

1. Indolent non-Hodgkin lymphoma
    - Follicular, marginal zone, small lymphocytic/CLL, lymphoplasmacytic lymphoma
        - Chemosensitive second to fourth chemotherapy failure (last time to progression <2 years)
    - Mantle cell lymphoma
        - First remission for high risk MIPI score, blastoid variant, or heavy blood/marrow involvement
        - Chemosensitive first chemotherapy failure

2. Aggressive non-Hodgkin lymphoma
    - Diffuse large B-cell or peripheral T-cell lymphomas
        - Chemosensitive relapse following HDCT/allogeneic SCT if time to relapse >1 year and age-adjusted IPI (AAIPI)=0–1
    - Lymphoblastic lymphoma
        - First remission after induction and CNS therapy if prior blood/marrow involvement and increased LDH
        - Chemosensitive first chemotherapy failure

3. Hodgkin lymphoma
    - Chemosensitive relapse following HDCT/allogeneic CT if time to relapse >1 year
4. Any lymphoma with indication for HDCT/ allogeneic SCT but unable to collect adequate autograft

Supportive Care in the Treatment of Lymphoma

Neutropenia Prevention

Primary or secondary prophylaxis to decrease the risk of febrile neutropenia and maintain chemotherapy dose intensity is indicated when treating with curative intent (e.g., preventing treatment delay/dose reduction). The recommendation for R-CHOP, ABVD, CODOX-M/IVAC, HyperCVAD, or intensive salvage therapy regimens, with or without rituximab (e.g., dexamethasone, high-dose cytarabine, cisplatin [DHAP]; ifosfamide, carboplatin, etoposide [ICE]; GDP; mesna rescue, ifosfamide, carboplatin, etoposide [MICE]; DICEP), in patients with aggressive Hodgkin or non-Hodgkin lymphoma older than 60 years of age, or poor prognostic factors (high IPI or IPS) is G-CSF 300 µg subcutaneous on days 8 and 12 of a 14- or 21-day chemotherapy regimen.

For primary prophylaxis of febrile neutropenic infection for similar indications above or co-morbidities that increase risk of infectious complications such as chronic obstructive pulmonary disease, or secondary prevention after a prior episode of febrile neutropenia:

- G-CSF 300 or 480 µg/day starting 3 days after chemotherapy completed until post-nadir absolute neutrophil count (ANC) >1.0 (usually 7–10 days)
- Must monitor CBC
- The alternative is one dose of pegfilgrastim (Neulasta) 6 mg on day 4 (without CBC monitoring, but at a cost of ~$2,500/dose)

Erythropoietin

Erythropoietin is not recommended because of evidence suggesting increased mortality rates. Consider only for symptomatic anemia patients who cannot receive red blood cell (RBC) transfusions (i.e., Jehovah's Witnesses, prior severe transfusion reactions or severe iron overload).

Antimicrobial Prophylaxis for Immunosuppressive Regimens

- Includes fludarabine, high dose cyclophosphamide, >5 days high dose corticosteroids every 21 days, especially with other immune suppressive agents such as bortezomib
- For immune-compromised patients (i.e., HIV, post-organ transplant or autoimmune disease patients who develop hematologic cancers) use prophylaxis during and for 3–6 months post-treatment
- *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis:
    - Choice 1: Septra 1 regular strength tab daily
    - Choice 2: dapsone 100 mg every Monday/Wednesday/Friday (or daily)
    - Choice 3: pentamidine 300 mg inhalation monthly
    - Choice 4: atovaquone 750 mg daily
- Shingles prophylaxis: valacyclovir 500 mg daily

Immunizations

Patients should be encouraged to keep all immunizations up to date. The reactivation and/or seroreversion of viruses that patients have been previously vaccinated against, such as hepatitis B, is a major cause of morbidity and mortality in patients with hematologic malignancies treated with

cytotoxic chemotherapy. Appendix G of the original guideline document outlines the general principles and specific immunization schedules for recipients of blood and marrow transplantations. See the National Guideline Clearinghouse summary of the CancerControl Alberta guideline Influenza immunization for adult and pediatric patients undergoing cancer treatment.

Family members and health care providers in contact with patients who have undergone a transplant should also be strongly encouraged to keep all immunizations up to date.

For patients who have experienced reactivation or seroreversion of hepatitis B virus, prompt administration of nucleoside/nucleotide analogues is essential. Lamivudine 100 mg/day during and for 3 months following R-CVP or R-CHOP chemotherapy for lymphoma is recommended for all patients who have a positive hepatitis B surface antigen test.

Follow-up Care in the Treatment of Lymphoma

The following late effects should be considered when patients are reviewed during follow-up:

Relapse

Careful attention should be directed to lymph node sites, especially if previously involved with disease.

Dental Caries

Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.

Hypothyroidism

After external beam thyroid irradiation to doses sufficient to cure malignant lymphoma, at least 50% of patients will eventually develop hypothyroidism. All patients whose thyroid-stimulating hormone (TSH) level becomes elevated should be treated with life-long thyroxine (T4) replacement in doses sufficient to suppress TSH levels to low normal.

Infertility

Multi-agent chemotherapy and direct or scatter radiation to gonadal tissue may cause infertility, amenorrhea, or premature menopause. However, with current chemotherapy regimens and radiation fields used, most patients will not develop these problems. All patients should be advised that they may or may not be fertile after treatment. In general, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer.

Secondary Neoplasms

Although quite uncommon, certain neoplasms occur with increased frequency in patients who have been treated for lymphoma. These include AML, thyroid, breast, lung, and upper gastrointestinal (GI) carcinoma, melanoma and cervical carcinoma *in situ*. It is appropriate to screen for these neoplasms by careful history, physical examination, mammography and Pap smears for the rest of the patient's life because they may have a lengthy induction period. Patients should be counseled about the hazards of smoking and excessive sun exposure, and should be encouraged to perform careful breast and skin examinations on a regular basis.

The table below outlines the minimum follow-up tests and examinations that should be performed on all patients after treatment for malignant lymphoma. Visits should be scheduled with an oncologist or family physician educated in post-treatment lymphoma surveillance every 3 to 4 months for 2 years, then every 6 months for 3 years, then annually.

Table. Minimum Follow-up Tests and Examinations for Patients with Malignant Lymphoma

Interval	Test
Every Visit	• Examination of lymph nodes, thyroid, lungs, abdomen, and skin • Complete blood count (CBC) and differential, lactate dehydrogenase (LDH) (consider erythrocyte sedimentation rate [ESR] and alkaline phosphatase for Hodgkin disease) • Consider chest X-ray during first 3 years for patients who previously had intrathoracic disease
Annually	• Thyroid-stimulating hormone (TSH) (if thyroid was irradiated)

Interval	Test
	• Mammogram for women after age 40 if irradiated (otherwise age 50) • Pap smear • Influenza immunization
Routine Body Computed Tomography (CT) Scanning	• After 3 months of therapy and if abnormal, again after completion of all therapy • If a residual mass is seen on the CT after completion of all therapy, then consider positron emission tomography (PET)/CT scan or consider a repeat CT scan 6 months later. Otherwise, no further routine CT scans are required

Clinical Algorithm(s)

The following clinical algorithms are provided in the original guideline document:

- Treatment algorithm for diffuse large B-cell lymphoma
- Treatment algorithm for follicular lymphoma
- Treatment algorithm for Hodgkin lymphoma

Scope

Disease/Condition(s)

Hodgkin and non-Hodgkin lymphoma

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Pathology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidelines for staging and management of Hodgkin and non-Hodgkin lymphomas

Target Population

Adults over 18 years of age with lymphoma

Note: These guidelines do not address lymphoma in the pediatric or adolescent populations. Different principles may apply to pediatric and adolescent patients.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Pathological classification of lymphoma (World Health Organization [WHO] classification scheme)
2. Immunohistochemical and fluorescence in situ hybridization (FISH) testing
3. Mandatory staging procedures
4. Restaging schedule

Treatment/Management

1. Treatment of diffuse large B-cell lymphoma (DLBCL) (chemotherapy ± involved field radiation therapy [IFRT], autologous stem cell transplantation [ASCT], central nervous system [CNS] prophylaxis)
2. Treatment of follicular lymphoma (IFRT, watchful waiting, chemotherapy, ASCT, allogeneic stem cell transplantation, radioimmunoconjugate therapy [RIT], palliative care)
3. Treatment of indolent lymphomas (treatment similar to follicular lymphoma)
4. Treatment of lymphoplasmacytic lymphoma (LPL) (plasmapheresis, chemotherapy, thalidomide, high-dose therapy supported by ASCT)
5. Treatment of special lymphomas (mantle cell, lymphoblastic, Burkitt's, gastric mucosa-associated lymphoid tissue [MALT], testicular, primary CNS, eye, cutaneous T-cell, aggressive T-cell, acquired immune deficiency syndrome [AIDS]-related, post-transplant lymphoproliferative disease [PTLD])
6. Treatment of Hodgkin lymphoma (chemotherapy, IFRT, extended field radiation, subtotal nodal irradiation [STNI], allogeneic stem cell transplantation)
7. Supportive care (prevention of neutropenia, antibiotics, immunizations)
8. Follow-up care

Major Outcomes Considered

- Complete response and overall response rates
- Time to disease progression
- Progression-free and overall survival
- Remission duration
- Freedom from treatment failure
- Fertility
- Toxicity of chemotherapy and radiation therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What are the diagnostic criteria for the most common lymphomas?
- What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma?

Search Strategy

Medical journal articles were searched using Medline (1950 to October Week 1, 2011), EMBASE (1980 to October Week 1, 2011), Cochrane Database of Systematic Reviews (3rd Quarter, 2011), and PubMed electronic databases. An updated review of the relevant existing practice guidelines for lymphoma was also conducted by accessing the websites of the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the European Society for Medical Oncology (ESMO), and the British Committee for Standards in Haematology.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Updated evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are

assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The draft guideline was circulated to all tumour team members for comment and approval, and all comments were reviewed by the tumour team lead and incorporated into the final version of the guideline, where appropriate. This updated guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate staging, management, and follow-up of patients with lymphoma

Potential Harms

- Adverse effects of chemotherapy and radiation therapy (xerostomia, severe nausea/vomiting, dental caries, febrile neutropenia, infertility, hypothyroidism, infections, leucopenia, thrombocytopenia, anemia, xerophthalmia, cataract formation)
- Complications of stem cell transplantation
- Rituximab is active in the treatment of Waldenström macroglobulinemia (WM) but associated with the risk of transient exacerbation of clinical effects of the disease and should be used with caution in patients with symptoms of hyperviscosity and/or immunoglobulin M (IgM) levels >40 g/L.

Contraindications

Contraindications

- Contraindications to radioimmunoconjugate therapy (RIT) include:
  - Greater than 25% marrow involvement
  - Impaired bone marrow reserve (platelet count <100 x 10^9/L)
  - Hypocellular bone marrow (≤15% cellularity; marked reduction in marrow precursors of 1 or more cell lines)
  - History of failed stem cell mobilization/collection
  - Prior external beam radiation to >25% active marrow
  - Human antimouse antibodies (HAMA)
  - Pregnant or breastfeeding patient
- Purine analogue therapy and chlorambucil should be avoided as initial therapy for transplant-eligible patients to prevent stem cell damage and decrease the risk of blood mobilization failure in the future.
- Live vaccines are contraindicated before ablation in recipients of hematopoietic stem cell transplant when significant marrow infiltration is present.
- Lumbar puncture is contraindicated in cases of intracranial hypertension and midline shift.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Lymphoma. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 86 p. (Clinical practice guideline; no. LYHE-002). [373 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Sep (revised 2013 Apr)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Hematology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Hematology Tumour Team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, nurse-practitioners, hematopathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Hematology Tumour Team. Lymphoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Sep. 78 p. (Clinical practice guideline; no. LYHE-002).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

In addition, a variety of resources, including chemotherapy regimens, general radiotherapy guidelines, prognostic models, a new lymphoma patient data sheet, ideal body weight charts, and principles of immunization, are available in the appendices to the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 19, 2012. The information was verified by the guideline developer on February 1, 2013. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab). This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014. This summary was updated by ECRI Institute on March 19, 2015 following the U.S. Food and Drug Administration advisory on Treanda (bendamustine hydrochloride).

Copyright Statement

Disclaimer

NGC Disclaimer